UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/658,698	09/08/2000	Samuel C Silverstein	60467/JPW/GJG	3655

7590 06/26/2003

John P. White, Esq.
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
VANDER VEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	12

DATE MAILED: 06/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/658,698	SILVERSTEIN ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 April 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

The Examiner in charge of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to F. Pierre VanderVegt, Ph.D. in Art Unit 1644.

Claims 33-132 have been canceled previously.

Claims 1-32 are currently pending.

Sequence Compliance

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence.

See, for example, page 37, line 25 (TPHPARIGL) of the instant specification.

Applicant is reminded of the sequence rules that require a submission for all sequences of more than 9 nucleotides or 3 amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences that require compliance with the rules.

Applicant is reminded to amend the specification and the claims accordingly.

Response to Arguments

2. Applicant's arguments with respect to claims 1-32 have been considered but are moot in view of the new ground(s) of rejection.

Claim Objections

3. Claims 1-32 are objected to because of the following informalities:

Base claim 1 recites in claim 1 "an Class I..." It is respectfully suggested to amend the claim to read --a Class I...--.

In claim 1, step d) recites "administering the antigen presenting cells (APCs) of step (c)," while the practice of claim c) results in the preparation of "Ag-APCs." Applicant is requested to clarify whether step d) is drawn to the use of the APCs before loading or the Ag-APCs after loading.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 17 are each vague and ambiguous in the recitation of "[a] method of delivering an antigen to an Class I MHC receptor to induce immunity against the antigen in a subject having a disease" in lines 1-3. It is not fully established by the claims whether the "antigen" is directly related to the "disease" suffered by the subject or whether the "subject having a disease" is merely a vehicle for inducing immunity to any "antigen." It is further unclear as to whether the "antigen" to which immunity is being induced is already present in the subject or whether the treatment is prophylactic in nature. Applicant should amend the claim to more clearly recite the relationship between the "antigen" and the "disease."

Claims 2 and 3 each recite the limitation "particle" in line 1 while base claim 1 recites "particles." There is insufficient antecedent basis for this limitation in the claim and Applicant should consistently use the plural form or the singular form of the term throughout claims.

Claim 5 recites the limitation "antigen presenting cell" in lines 1-2 while base claim 1 recites "antigen presenting cells." There is insufficient antecedent basis for this limitation in the claim and Applicant should consistently use the plural form or the singular form of the term throughout claims.

Claim 8 recites the limitation "crude cell extract" in line 2. There is no antecedent basis for this limitation in the claim. It is respectfully submitted that a "crude cell extract" is not commensurate with the recitation of "the antigen," as the extract is a mixture of a plethora of antigens and not a single antigen.

Claim 14 recites the limitation "cancerous tumor" in line 2. There is no antecedent basis for this limitation in the claim. Base claim 1 recites in lines 1 and 2 "delivering an antigen to an Class I MHC receptor to induce immunity to the antigen..." It is respectfully submitted that a "cancerous tumor" is not commensurate with the recitation of "an antigen" or "the antigen," as a tumor presents a plethora of antigens to the immune system and not a single antigen.

Claim 15 recites the limitation "bacterial infection or a viral infection" in line 2. There is no antecedent basis for this limitation in the claim. Base claim 1 recites in lines 1 and 2 "delivering an antigen to an Class I MHC receptor to induce immunity to the antigen..." It is respectfully submitted that neither a bacterial infection nor a viral infection is commensurate with the recitation of "an antigen" or "the antigen," as an infection is a term describing a physical state, not an antigen.

Claims 18 and 19 each recite the limitation "particle" in line 1 while base claim 1 recites "particles." There is insufficient antecedent basis for this limitation in the claim and Applicant should consistently use the plural form or the singular form of the term throughout claims.

Claim 21 recites the limitation "antigen presenting cell" in lines 1-2 while base claim 17 recites "antigen presenting cells." There is insufficient antecedent basis for this limitation in the claim and Applicant should consistently use the plural form or the singular form of the term throughout claims.

Claim 24 recites the limitation "crude cell extract" in line 2. There is no antecedent basis for this limitation in the claim. It is respectfully submitted that a "crude cell extract" is not commensurate with the recitation of "the antigen," as the extract is a mixture of a plethora of antigens and not a single antigen.

Claim 30 recites the limitation "cancerous tumor" in line 2. There is no antecedent basis for this limitation in the claim. Base claim 17 recites in lines 1 and 2 "delivering an antigen to an Class I MHC receptor to induce immunity to the antigen..." It is respectfully submitted that a "cancerous tumor" is not commensurate with the recitation of "an antigen" or "the antigen," as a tumor presents a plethora of antigens to the immune system and not a single antigen.

Claim 31 recites the limitation "bacterial infection or a viral infection" in line 2. There is no antecedent basis for this limitation in the claim. Base claim 17 recites in lines 1 and 2 "delivering an antigen to an Class I MHC receptor to induce immunity to the antigen..." It is respectfully submitted that neither a bacterial infection nor a viral infection is commensurate with the recitation of "an antigen" or "the antigen," as an infection is a term describing a physical state, not an antigen.

5. Claims 1-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Briefly, the claims are most broadly drawn to a method of inducing an immune response in a subject having a disease to an antigen. The method includes a) loading the antigen and adenosine triphosphate into a particle, b) coating the particle with a ligand of antigen presenting cells, c) incubating the coated particles with antigen presenting cells (APCs), and d) administering the APCs to the subject and generating an immune response to the antigen.

In the "First Series of Experiments" at pages 32-34 and Table 1 on page 35 of the specification it is disclosed that dendritic cells primed in this manner were capable of stimulating the proliferation of T

cells in a standard *in vitro* thymidine-uptake assay, asserting that the assay represent a "CTL assay" at page 35, lines 1-7. However, CTL activity as a measure of specific cellular immunity is more accurately reflected by a cytotoxicity assay, such as a ^{51}Cr-release assay or a cytokine profile. It is well established in the art that cellular immunity, mediated by NK cells and killer T cells, is a Type 1 activity and that humoral immunity, mediated by antibodies, is a Type 2 activity (see, *e.g.*, page 188, column 1 of Grufman et al (U on PTO-892)).

It is respectfully submitted that it would require an undue amount of experimentation on the part of one skilled in the art to practice the claimed invention. Grufman et al in the paragraph bridging the columns on page 1088 discloses that IL-12 is required for Type 1 responses to cancer antigens and some bacterial antigens, while not being crucial for some other bacterial infections or viral infections. The la Sala et al 2001 reference (V on PTO-892) discloses that incubating dendritic cells in ATP during maturation, *i.e.*, antigen loading, distorts said maturation and inhibits the production of IL-12 by the matured dendritic cells and impairs their ability to initiate Type 1 immune responses *in vitro* (abstract and column 1 of page 1614 in particular). Accordingly, based upon the state of the art, the artisan would not be able to predict that the dendritic cells generated by the claimed method would be able to stimulate an effective killer T cell response to any antigen in vivo, irrespective of whether the T cells are stimulated by the dendritic cells *in vivo* (claims 1-16) or *in vitro* (claims 17-32).

Additionally, and in particular regard to the method of claims 1-16, the specification does not demonstrate, or reasonably suggest success of, the ability of those same dendritic cells to attract cytotoxic T cells *in vivo*. The la Sala *et al* 2002 reference (W on PTO-892) discloses that dendritic cells that are treated with extracellular ATP possess a reduced capacity for attracting Th1 and T-cytotoxic (killer) 1 cells. One skilled in the art would not be able to predict that dendritic cells which were primed in vitro in the presence of extracellular ATP would be able to attract Type 1 killer T cells *in vivo* for activation versus the loaded antigen.

In view of the lack of predictability in the art to which the invention pertains and the lack of established clinical protocols for therapies based upon the *in vivo* or *in vitro* activation of T cells using artificially manipulated APCs, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inducing a cytotoxic response to an antigen *in vivo*.

Conclusion

7. No claim is allowed.

8. In view of the new grounds of rejection, this action is made **NON-FINAL**.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (703) 305-4441. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-3014.Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
June 20, 2003

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
6/24/03